REMARKS AND ARGUMENTS

I. SPECIFICATION

The Examiner has objected to the specification as containing embedded hyperlinks. Applicants have amended the specification to delete the hyperlinks and to comply fully with MPEP §608.01. The Examiner has objected to the specification as containing blank spaces. Applicants have spoken with the Examiner and respectfully request that the blank spaces or pages on pages 22, 24, 26, 28, 30, 32, 34, 36, 38, 40-44, 46, and 48-50 be removed. If the Examiner feels that this will not overcome these informalities, Applicants are willing to submit a substitute specification under 37 C.F.R. 1.125 (MPEP §608.01 (q)).

II. REJECTIONS

The Rejection under 35 U.S.C. § 101/112, first paragraph.

The Examiner has rejected Claims under 35 U.S.C. § 101/112 first paragraph, as allegedly being unsupported by a substantially asserted utility. The Examiner alleges that the specification has not established a specific and/or well-established utility for the Bolekine polypeptide (SEQ ID NO:2). Applicants respectfully traverse the rejection.

The Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed. However, when the condition to be diagnosed is specifically identified, the asserted utility is "specific".

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in Brenner v. Manson, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that

products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. § 2107.01, emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility".

The MPEP 2107.01 refers to Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980) where the court reversed a finding by the Office that the applicant had not set forth a "practical" utility under 35 U.S.C. §101. The facts in Bowler are particularly relevant to the instant rejection. In Nelson, two experiments were relied on to provide utility, a rat blood pressure test (BP) and a gerbil colon smooth muscle stimulation test (GC-SMS). The Nelson inventors were using these tests on novel compounds and comparing the results to natural control prostaglandins PGF alpha and PGE1. In the BP test, the blood pressure of anesthetized rats was recorded by polygraph to determine if a novel compound would have a lowering or elevating effect on blood pressure when compared with PGE1. Two novel compounds tested positive in this test, and at trial, testimony was given on the reliability of the BP test, with a scientist stating that it had been in use between five and six years and had produced excellent results. The GC-SMS test was an *in vitro* test comprising excising a section of colon from a gerbil, and connecting a lever arm that would measure the contraction of the smooth muscle in response to a novel compound. Again, a naturally occurring PGE was used as a positive control. The same novel compounds that tested positive in the rat BP assay also tested positive in the GC-SMS test. The USPTO Board of Interferences characterized these tests as "rough screens, uncorrelated with actual utility" and rejected the utility based on these tests. The court found the Board erred in not recognizing that tests providing evidence of a pharmacological activity yield a practical utility even though they may not establish a specific therapeutic use. The Nelson court found "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public" and "Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility." Thus the Nelson court overturned the Board and found for utility.

The legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in Cross v. Iizuka, 753 F.2nd 1040, 224 USPQ 739 747-48 (Fed Cir. 1985). In Iizuka, the assay used was a platlet microsome assay, consisting of an *in vitro* milieu consisting of blood platelets and other finely granular elements of protoplasm, such as ribosomes, fragmented endoplasmic reticula and mitochondrial cristae. In Iizuka, the Federal Circuit found an *in vitro* assay, the inhibition of thromboxane synthetase in human or bovine platelet microsomes, satisfied the utility requirement:

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."

Thus, *in vitro* assays in both Nelson and Iizuka were held to be valid for satisfying the utility requirement.

The Federal Circuit relied on Iizuka and Nelson in their holding on finding that *in vitro* results provide for utility, although the Examiner had rejected the asserted utility as not predictive of an *in vivo* response in Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ2d 1985 (Fed. Cir. 1996). Fujikawa sought to invalidate the Wattanasin application in an interference proceeding in front of the Board. One of Fujikawa's arguments was that the Wattanasin application had no utility. The Board determined that Wattanasin had reduced the invention to practice when several of their cholesterol inhibiting compounds showed positive results *in vitro*. The Board relied on expert testimony from both parties, especially that of the Fujikawa expert who stated that there was a reasonable doubt that some elements may be active *in vitro*, but inactive *in vivo*. Fujikawa relied on this testimony to prove that *in vitro* tests provided no practical utility. The Board rejected this argument and the Federal Circuit affirmed the decision of the Board stating "Of course it is possible that some compounds active *in vitro* may not be active *in vivo*. But as our predecessor court in Nelson explained, **a 'rigorous correlation' need not be shown in order to establish practical utility: 'reasonable correlation' suffices.**" (Emphasis Added) Even the Fujikawa expert admitted to the court that such a "reasonable correlation" existed. Fujikawa also cited two papers that claimed that no reliable relationship existed between *in vitro* and *in vivo* results in cholesterol inhibiting compounds. The Federal Circuit disagreed, finding that the cited art taught while *in vitro* testing is sometime not a good indicator of *in vitro* potency, it did imply that that compounds which are active *in vitro* will exhibit some *in vivo* activity.

The Fujikawa holding was used in a non-precedential opinion of the Board in ex parte Davies, (Appeal No. 95-3746, Application No. 08/063,431 - Now U.S. Patent No 5,262,428, 1999). Applicants

cite this opinion as the facts are very close to the instant case. In Davies, the Applicants claimed methods for treating mammals with a compound that would selectively block the uptake of serotonin (5-HT) or dopamine. The Applicants disclosed treating diseases such as Parkinson's Disease in the specification. The Applicants provided *in vitro* data which showed that the compound was useful in the blocking of serotonin and dopamine uptake. The Examiner argued that data had no utility as it was not inexorably linked to the treatment of a particular disease. The Examiner also argued that the Applicants had not shown that their *in vitro* tests indicated *in vivo* activity. The Board rejected both arguments finding that the uptake of serotonin and dopamine were pharmacological activities, and quoted Fujikawa; "practical utility may be shown by adequate evidence of any pharmacological activity." The Board similarly held the utility requirement was met in the non-precedential decisions of Ex Parte Siler-Khodr (Appeal No. 1996-2468/ Application 08/091,899) and Ex parte Hofmann (Appeal No. 1996-0729/Application No. 07/859,572).

Applicants submit that these holdings help to determine patentable utility. The courts and the Board have held that *in vitro* assays do support utility, even though they may be removed from direct clinical application. The *in vitro* data submitted by the Applicant uses an assay well known in the art to provide a "pharmacological activity" that is "reasonably correlated" with the scope of the claims asserted by the Applicants. Applicants believe the MLR and vascular permeability assays fulfill the requirements proposed in Nelson, Iizuka and Fujikawa. The Applicants have submitted the non-precedential opinions of the Board to point out the reasoning that the Board uses in applying these cases, and the data provided by other applicants to provide utility for their inventions.

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. § 2107 II (B)(1)(ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974).

See, also In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); In re Irons, 340 F.2d 974, 144 USPQ 351 (1965); In re Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner makes a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift back to the applicant.

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

The Biology at issue.

In support of the rejection, the Examiner cites scientific papers from Kahan et al., Curr. Opin. Immuno. 4: 553-560(1992). Applicants respectfully submit the Kahan paper cannot be relied on to find a lack of utility. The Examiner cites the Kahan article to assert that no *in vitro* immune assay predicts or correlates with in vivo immunosuppressive efficacy, thus supporting the rejection of utility based on the MLR assay. Applicants find that according to Kahan, there are **no** means of assaying for immunosuppressive efficacy, including clinical trials. From Kahan at page 558: "Of the numerous obstacles currently hindering the development of efficacious immunosuppressive regimens, the lack of methodology for clinical transplantation trials is of particular importance. To date, no series of Phase I and II toxicity and dose-finding trials has been conducted in order to establish a foundation for clinical investigation." (Emphasis added) Applicants submit that even if they had included Phase I and II clinical trial data in the instant application, then according to Kahan, this data would not have utility. Applicants find that the goal of Kahan is to present data and ask for guidelines on clinical trials, as stated in the last line of his abstract on page 553: "The availability of this array of potential agents highlights the need to develop guidelines for clinical trial methodologies to address the unique needs and demands of organ transplantation." Applicants submit this places Kahan outside of the scope of relevant prior art. Kahan does not review the MLR itself, and the assay is placed together will all immune *in vitro* assays in his conclusion that "no *in vitro* immune assay" is useful. Such a broad generalization is not a compelling reason to reject the Applicant's use of the MLR to provide utility.

Applicants have also provided herewith a representative number of patents that have been allowed under the new utility guidelines and have used the MLR in support of utility for their inventions. Applicants are aware that the examination of each application is done on the merits, but wish to point out that the MLR is still very much in use. Patent holders using the MLR assay include Immunex (US), Erasmus University (NL), Thomas Jefferson University (US), Dana Farber (US) and the CDC (US) and NIH (US). The CDC and NIH both approve of the MLR stating that: "MLR assays or 'mixed lymphocyte response' assays are the standard *in vitro* assay of antigen presenting function in cellular immunity."(US 6,472,518- column 20, lines 21-23 and US 6,734,014 - column 21, lines 16-18). (Applicants have provided the patents in their entirety on CD.) Thus, Applicants wish to point out that the MLR is being used by those of skill in the art under the new utility guidelines.

A scientific reference that the Applicants would like to cite is the paper by Rashid et al. (Rashid G., *In vivo* 3: 279-284 (1989)). Rashid's hypothesis was that plasmocytomas may suppress the immune response. To prove this, plasmocytoma cells were injected into mice and the rate of mortality determined that 50% of the mice had died within 25 days of inoculation and 100% had died within 32 days. To show that this mortality was linked to immune suppression, Rashid used splenic T cells from tumor bearing mice and assayed them in a MLR assay containing normal effector spleen cells. The T cells from the plasmocytoma bearing mice suppressed the MLR response of the normal splenic cells. Rashid conducted this experiment in quadruplicate, taking T-cells from mice at 17, 18, 21 and 24 days after plasmocytoma cell injection. Immune suppression was seen at all 4 time points (please see Table III of the paper and left column page 281). The Applicants cite this paper as evidence that the MLR as an in vitro assay can be linked to in vivo result. In the Rashid paper, the investigators are using a mouse tumor model in conjunction with the MLR to show immune suppression, thus linking mortality with immune suppression. Applicants submit that this is a credible and substantial use of the MLR in linking *in vivo* and *in vitro* results.

The MLR data for the instant application is disclosed in Example 10 of the specification, beginning at page 87. The Examiner has taken exception to the results disclosed in the specification alleging that the speciation fails to provide any data or evidence of the results of the assay, and alleges that there is no statistical support for the Applicants conclusion. The data for bolekine is listed on page 87, lines 35-37 of the specification. This data states that a concentration of 12.40 nM of Bolekine in the MLR assay resulted in a 112.0% increase over control and Bolekine at a concentration of 124.00 nM resulted in an 192.7% increase over control. The MLR as assayed is repeated in triplicate for each protein

lot of Bolekine, thus confirming that T-cell stimulation by Bolekine is a consistent result. Therefore, these results are strongly positive.

The Applicants support the utility of Bolekine with a second *in vivo* immunological assay. Disclosure of the Skin Vascular Permeability assay is disclosed in Example 11 of the specification on page 88 of the specification. This assay is also known as the Miles assay. In brief, a protein that is believed to have a chemoattractant activity for immune cells is injected into the backs of hairless guinea pigs. Evans Blue dye is used as a tracer. If the molecule is an immune cell chemoattractant then they will extravasate from the vasculature and into the surrounding area. If the molecule is scored as positive, then the guinea pigs are sacrificed and the skin is sectioned for histopathologic evaluation. The skin sections are then evaluated for what types and how many immune cells have migrated to the site of injection. The Bolekine polypeptide was strongly positive in this assay.

In support of the instant application, Applicants have submitted a declaration under 37 C.F.R. §1.132 from Dr. Sherman Fong in support of the MLR assay and the Vascular Permeability Assay. This provides further support for the utility for the Bolekine polypeptide and its uses. The declarations contain step-wise descriptions for performing the assays and provide the rational for performing the assays. They also provide scientific references from other investigators that use these assays in their research and how to interpret the results obtained from that assay.

Applicants have disclosed in the specification that Bolekine has the primary sequence structure of a chemokine. Applicants have found the Bolekine has chemokine activity in vivo and in vitro assays that test immune cell proliferation and function. The assertion of Bolekine utility in the specification is that Bolekine can be used to limit tumor growth or to activate immune cells in treating infection beginning on page 70:

> As chemokines that lack the ELR motif such as Bolekine, are angiostatic (Strieter RM. et al. Journal of Biological Chemistry 1995; 270: 27348-27357), then Bolekine may be useful in treating tumors by inhibiting the neovascularization that accompanies tumor growth. Admistration of the Bolekine polypeptide either alone or in combination with another angiostatic factor such as anti-VEGF, may prove useful in limiting or reducing tumor growth.
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> Chemokines may be able to activate immune cells, as shown with the CXC chemokines activation of neutrophils (Baggiolini et al. Adv Immunology 1994; 55:97-179), and the non-CXC chemokines are mainly chemotactic for T lymphocytes. Bolekine may be useful in treating infection, as local administration of the polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing the infection at a faster rate.

Applicants have included later published papers that confirm these functions. In later published literature, Bolekine is known as CXCL14 or BRAK. In a paper by Shurin et al., they confirm the Applicant's MLR result by performing their own MLR assay and also finding that CXCL14/BRAK/Bolekine is an immune

cell chemoattractant (See page 5495, Shurin et al., J. Immunol. 174(9): 5490-5498 (2005)). Shurin et al., also describes how loss of CXCL14/BRAK/Bolekine is correlated with more aggressive tumors. Fredrick et al., observered that CXCL14/BRAK/Bolekine expression was absent in a number of tumor lines and primary tumors (Fredrick et al., Am. J. Path. 156(6) 1937-1950 (2000)). Fredrick et al., also describes that was expressed on infiltrating inflammatory cells (see Figure 6 and Tables 1-3). Another group determined that CXCL14/BRAK/Bolekine had an anti-tumor effect (Schwarze et al., Prostate 64(1): 67-64 (2005). Schwarze transfected CXCL14/BRAK/Bolekine into prostate tumor cells and injected into mice had a 38% or 43% reduction in tumor volume than tumor cells transfected with vector alone. Shellenberger et al., found CXCL14/BRAK/Bolekine is a chemoattractant and also found it absent in a number of primary tumors, hypothesizing that loss of this gene either allowed greater angiogenesis or less infiltration of immune cells (Shellenberger et al., Cancer Res. 64:8262-8270(2004)). Sleeman et al., confirmed the Applicant's results by cloning the murine form of CXCL14/BRAK/Bolekine and subjecting it to migration and inflammatory assays (Sleeman et al., Inter. Immuno. 12(5):677-689 (2000)). This group found that CXCL14/BRAK/Bolekine was chemotatic for a B cell lymphoblastoid line and a monocytic cell line (See Figure 8, page 684, and Results, page 686). The murine form of CXCL14/BRAK/Bolekine also caused the migration of inflammatory cells *in vivo*. Sleeman et al., injected the murine form of CXCL14/BRAK/Bolekine subcutaneously into the foot pad of mice, and found that this caused a infiltration of mononuclear and polymorphonuclear cells. This result is the same as the Applicant's result of injecting CXCL14/BRAK/Bolekine into the back of hairless guinea pigs as described in the specification.

Applicants request that in light of the data submitted in the original specification, the decisions of the courts and the USPTO Board in their holdings on in vitro utility, the Fong declarations, and scientific literature, the rejection under 35 U.S.C. § 101/§112 first paragraph be withdrawn.

SUMMARY

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

Should the Examiner not agree that all claims are allowable, then a personal or telephonic interview is respectfully invited to discuss any remaining issues and accelerate the eventual allowance of this application.

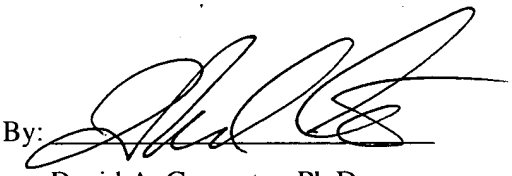
No fee is believed to be due for the submission of this response. Should any fees be required, however, please charge such fees to Genentech, Inc.'s Deposit Account No. 07-0630.

Respectfully submitted,

GENENTECH, INC.

#191865

Date: October 26, 2005

By: 

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